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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/994,425	11/26/2001	Henry C. Chiou	TTI-143CPCN2	1389

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/994,425	CHIOU ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/10/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed November 26, 2001 has been entered. Claims 1-30 have been cancelled. Claims 31-46 have been newly added.

Accordingly, Claims 31-46 are pending in the instant application.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

The preliminary amendment filed November 26, 2001 includes an amendment to the first sentence of the specification but the filing date for the 09/374,434 application is incorrect and the status of each application is not included.

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the **relationship** (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The **status** of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Specification

The disclosure is objected to because of the following informalities:

There is a discrepancy between the description in the specification on p. 4 for plasmids pJ7ΩhIFNαSB and pJ7ΩhIFNα-nonSB and the maps of these plasmids in Figures 7 and 8. The description on p. 4 states that both pJ7ΩhIFNαSB and pJ7ΩhIFNα-nonSB have an SV40 small t intron (IVS) located immediately upstream of the interferon gene. However, the figure shows the element downstream from the gene. Also, not included in the description of the plasmids but included in the figures is the β-globin IVS located between the TBG promoter and the coding sequence for the interferon gene. The description given for the two plasmids on p. 17 of the specification is the same as the description on p. 4, indicating that the SV40 small t intron (IVS) is located immediately upstream of the interferon gene.

Appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31, 33-36, 37, and 39-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31, 36, 37, 40, 41 are indefinite in their recitation of "[a]n expression vector" because the term "expression vector" implies that the vector will include a gene of interest that is to be expressed and that the gene of interest will be operably linked to the promoter and enhancer elements recited in the claim, but the instant claims do not require the presence of a gene of interest or protein coding sequence.

Claims 33-35 are indefinite in their recitation of "the gene" because the phrase has ambiguous antecedent basis as the claims refer to "different genes" (in Claim 31) and "the coding sequence of a

gene" (in Claim 32) and thus it is unclear to which gene "the gene" refers to in the phrase "wherein the gene encodes a human interferon protein."

Claims 36 and 40-46 are indefinite in their recitation of a "thyroid binding globulin promoter" because neither the art nor the instant specification disclose a "thyroid binding globulin." Rather, both the art and the instant specification disclose a "thyroxine binding globulin promoter." The art also refers to the "thyroid hormone-binding globulin promoter."

Claim 39 is indefinite in its recitation of "wherein the intron is located within the leader sequence of the gene" because "the leader sequence of the gene" lacks antecedent basis. The gene referred to in Claim 32 does not have and is not required to have a "leader sequence."

Claims 39 and 43 are indefinite in their recitation of a "leader sequence" because the term is not defined in the specification and the term has a number of specific meanings in the art, depending on the context. Thus, the metes and bounds of the claim are not clearly set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31 and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Su et al. (1996, Human Gene Therapy 7(4): 463-470).

Claim 31 is drawn to an expression vector comprising a liver-specific promoter and a liver-specific enhancer, wherein said promoter and enhancer are derived from different genes. Claim 32 is

drawn to the expression vector of Claim 31, wherein the promoter and enhancer are located upstream from the coding sequence of a gene.

Su et al. (1996) disclose an expression vector comprising a liver-specific promoter and a liver-specific enhancer. The enhancer is the human alpha-fetoprotein (AFP) enhancer and the promoter is the albumin promoter. Both the enhancer and the promoter are liver-specific elements.

Thus, the claimed invention is disclosed in the prior art.

Claims 31 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Chow et al. (1991, J. Biol. Chem. 266(28): 18927-18933).

Chow et al. (1991) disclose an expression vector comprising the mouse metallothionein I promoter in combination with the enhancer element of the human prothrombin gene (see abstract and page 18931, column 1, paragraph 1). Metallothionein I is a protein that is synthesized in the liver. Both the promoter and enhancer are liver-specific elements.

Thus, the claimed invention is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of

each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Su et al. (1996), Perillo et al. (1990, New England J. of Med. 323: 295-301), Streuli et al. (1980, Science 209: 1343-1347), and Gewert et al. (1993, J. of Interferon Research 13: 227-231).

Claim 31 is drawn to an expression vector comprising a liver-specific promoter and a liver-specific enhancer, wherein said promoter and enhancer are derived from different genes. Claim 32 is drawn to the expression vector of Claim 31, wherein the promoter and enhancer are located upstream from the coding sequence of a gene. Claim 33 is drawn to the expression vector of Claim 32, wherein the gene encodes a human interferon protein. Claim 34 is drawn to the expression vector of Claim 33, wherein the human interferon protein is IFN-α. Claim 35 is drawn to the expression vector of Claim 33, wherein the gene encodes a human IFN-α2b protein.

Su et al. (1996) disclose an expression vector comprising a liver-specific promoter and a liver-specific enhancer operably linked to the herpes simplex virus thymidine kinase gene (HSV-TK). The enhancer is the human alphafetoprotein (AFP) enhancer and the promoter is the albumin promoter. Both the enhancer and the promoter are liver-specific elements. Su et al. further discloses that when the construct was used to produce transgenic mice, the TK gene was expressed predominantly in the liver.

Perrillo et al. (1990) disclose that IFN-α2b therapy is effective for the treatment of chronic hepatitis B infection.

Streuli et al. disclose the DNA sequence of the cDNA clone Hif-SN206 which they designate as IFN-α2 (see abstract and Col. 3, paragraph 1) and Gewert et al. disclose that this particular gene is actually the subtype IFN-α2b and further describes explicitly the differences in the sequences of IFN-

α2a, IFN-α2b, and IFN-α2c (see Col. 1, paragraph 2 to Col. 2). Streuli et al. and Gewert et al. do not describe the inclusion of these interferon genes in expression vectors of the type instantly claimed.

Since interferon is well-known for its antiviral activity and IFN-α2b in particular is the only agent licensed in the United States for the treatment of chronic HBV infection one would have been motivated to develop vectors for the delivery of an interferon gene to a hepatocyte either *in vitro* or *in vivo*. The skilled artisan would have been motivated to use a vector that provides for liver-specific expression of the interferon gene, such as the one described by Su et al. Thus, the skilled artisan would have been motivated to include the IFN-α2b gene in place of the HSV-TK gene in the vector of Su et al. Such a vector could then be used to test the effect of delivering the interferon gene to a hepatocyte infected with hepatitis B. The skilled artisan would have anticipated a reasonable expectation for successfully producing the interferon encoding vector because only standard molecular biology techniques are need to prepare the vector.

One would have been motivated to combine the teachings of Su et al., Perillo et al., Streuli et al., and Gewert et al. in order to produce liver-specific expression vectors encoding interferon.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chow et al. (1991) and Rouet et al. (1992, J. Biol. Chem. 267(29): 20765-20773), Perillo et al. (1990), Streuli et al. (1980), and Gewert et al. (1993)

Claim 37 is directed to an expression vector comprising the liver-specific alpha-1 microglobulin/bikunin enhancer and a liver-specific promoter from a different gene. Claim 38 is directed to an expression vector comprising a liver-specific promoter and a liver-specific enhancer, wherein the promoter and enhancer are from different genes and both are located upstream from the coding sequence

of a gene, and wherein the vector further comprises one or more introns located (a) downstream from the promoter and enhancer and (b) upstream from the coding sequence.

Chow et al. (1991) disclose an expression vector comprising the mouse metallothionein I promoter in combination with the enhancer element of the human prothrombin gene (see abstract and page 18931, column 1, paragraph 1). Metallothionein I is a protein that is synthesized in the liver. Both the promoter and enhancer are liver-specific elements. The reference further discloses that the metallothionein promoter is a strong liver-specific promoter (p. 18931, column 1, paragraph 1).

Rouet et al. (1992) disclose that the α1-microglobulin/bikunin precursor (ABP) gene includes a potent enhancer element that confers liver-specific expression. The enhancer functions with heterologous promoters in a position- and distantce-independent fashion (see abstract). The reference further discloses that the combination of a weak promoter and a strong distant and liver-specific enhancer distinguishes the ABP gene from most other plasma protein genes expressed in hepatocytes (see abstract).

Perrillo et al. (1990) disclose that IFN-α2b therapy is effective for the treatment of chronic hepatitis B infection.

Streuli et al. disclose the DNA sequence of the cDNA clone Hif-SN206 which they designate as IFN-α2 (see abstract and Col. 3, paragraph 1) and Gewert et al. disclose that this particular gene is actually the subtype IFN-α2b and further describes explicitly the differences in the sequences of IFN-α2a, IFN-α2b, and IFN-α2c (see Col. 1, paragraph 2 to Col. 2). Streuli et al. and Gewert et al. do not describe the inclusion of these interferon genes in expression vectors of the type instantly claimed.

Since interferon is well-known for its antiviral activity and IFN-α2b in particular is the only agent licensed in the United States for the treatment of chronic HBV infection one would have been motivated to develop vectors for the delivery of an interferon gene to a hepatocyte either *in vitro* or *in vivo*. The skilled artisan would have been motivated to use a vector that provides for liver-specific expression of the interferon gene, and would have been further motivated to achieve high-level expression by combining a

strong liver-specific enhancer, such as the ABP enhancer, with a strong liver-specific promoter, such as the metallothionein promoter, particularly in view of the fact that Rouet et al. point out that the ABP promoter is a weak promoter. Thus, the skilled artisan would have been motivated to produce an expression vector comprising the metallothionein promoter and the ABP enhancer operably linked to the coding sequence of the IFN-α2b gene. Such a vector could then be used to test the effect of delivering the interferon gene to a hepatocyte infected with hepatitis B. The skilled artisan would have anticipated a reasonable expectation for successfully producing the interferon encoding vector because only standard molecular biology techniques are need to prepare the vector and the art had already shown that the ABP enhancer functions well with heterologous promoters. Likewise, the art had also already shown that the metallothionein promoter functions well with heterologous enhancer elements.

One would have been motivated to combine the teachings of Chow et al., Rouet et al., Perillo et al., Streuli et al., and Gewert et al. in order to produce liver-specific expression vectors encoding interferon.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 40, 42, and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashi et al. (1993, Molecular Endocrinology 7(8): 1049-1060) and Rouet et al. (1992, J. Biol. Chem. 267(29): 20765-20773), Perillo et al. (1990), Streuli et al. (1980), and Gewert et al. (1993).

The claims are directed to an expression vector comprising the human thyroxine-binding globulin (TBG) promoter and the ABP enhancer.

Hayashi et al. (1993) disclose that the human thyroxine-binding globulin (TBG) gene contains a liver-specific promoter.

Rouet et al. (1992) disclose that the human α1-microglobulin/bikunin precursor (ABP) gene includes a potent enhancer element that confers liver-specific expression. The enhancer functions with heterologous promoters in a position- and distantce-independent fashion (see abstract). The reference further discloses that the combination of a weak promoter and a strong distant and liver-specific enhancer distinguishes the ABP gene from most other plasma protein genes expressed in hepatocytes (see abstract).

Perrillo et al. (1990) disclose that IFN-α2b therapy is effective for the treatment of chronic hepatitis B infection.

Streuli et al. disclose the DNA sequence of the cDNA clone Hif-SN206 which they designate as IFN-α2 (see abstract and Col. 3, paragraph 1) and Gewert et al. disclose that this particular gene is actually the subtype IFN-α2b and further describes explicitly the differences in the sequences of IFN-α2a, IFN-α2b, and IFN-α2c (see Col. 1, paragraph 2 to Col. 2). Streuli et al. and Gewert et al. do not describe the inclusion of these interferon genes in expression vectors of the type instantly claimed.

Since interferon is well-known for its antiviral activity and IFN-α2b in particular is the only agent licensed in the United States for the treatment of chronic HBV infection one would have been motivated to develop vectors for the delivery of an interferon gene to human hepatocytes either *in vitro* or *in vivo*. The skilled artisan would have been motivated to produce a vector that provides for liver-specific expression of the interferon gene, and would have been further motivated to achieve high-level expression by using a strong liver-specific enhancer, such as the human ABP enhancer, with a heterologous promoter, in view of the fact that Rouet et al. point out that the ABP promoter is a weak promoter. In selecting a heterologous promoter, the skilled artisan would have been motivated to choose a liver-specific promoter of human origin, such as the human TBG promoter, so that the vector would be optimized for use in human hepatocytes. Thus, the skilled artisan would have been motivated to produce an expression vector comprising the TBG promoter and the ABP enhancer operably linked to the coding sequence of the IFN-α2b gene. Such a vector could then be used to test the effect of delivering the

interferon gene to a human hepatocyte infected with hepatitis B. The skilled artisan would have anticipated a reasonable expectation for successfully producing the interferon-encoding vector because only standard molecular biology techniques are need to prepare the vector and the art had already shown that the ABP enhancer functions well with heterologous promoters.

One would have been motivated to combine the teachings of Hayashi et al., Rouet et al., Perillo et al., Streuli et al., and Gewert et al. in order to produce a liver-specific expression vector encoding interferon for use in humans or human cells.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (571) 272-0548.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER